REMARKS

Reconsideration of this application is requested. Claims 1-26 are in the case. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

I. ELECTION/RESTRICTION

In response to the Restriction Requirement set forth on page 2 of the action, the Applicants hereby elect Group II (Claims 1-20). This election is made with traverse.

At the top of page 2 of the action, the Examiner has noted the Applicants' election of Example 2. The Examiner has used this election of species as a reference point for the Examiner to create a "natural genus" based on a "liberal interpretation" of the doctrine of legal and chemical equivalence. The Examiner has further stated that that restriction will now be required pursuant to 35 U.S.C. 121 and 372.

On page 3 of the action, the Examiner has determined, without consulting with the Applicants, that Group I will be examined since, according to the Examiner, the Applicants' election of species falls within Group I. In light of this, Claim 2 and the unelected portions of Claims 1 and 3-20 have been withdrawn from further consideration as allegedly drawn to a non-elected invention.

The reasoning presented in the Restriction Requirement is not fully understood by the Applicants. Group II encompasses all of the subject matter of Group I and it is not seen why these two groups have been suggested. It is believed, therefore, that Claims 21-26 should be examined along with Claims 1-20 of elected Group II.

It is believed that Group II is the same invention as defined by Groups III to VII. Claims 1-20 share a "special technical feature" with the compounds of Claims 21-26 in that all compounds are based upon 3,7-diazabicyclo[3.3.1]nonane compounds (bispidines) that bear a C_{1-3} alkyl substituent in one or more of the 2-, 4-, 6- and 8-positions (see, for example, page 58, lines 18-21 of the present application). Moreover, the elected species (the compound of Example 2) reads onto Claim 2, as the definition of R^1 in that claim covers saturated, branched C_{1-8} alkyl groups, such as the *tert*-butyl group of the compound of Example 2). The elected species there falls within the Group II and **not** Group I, as the latter group excludes the compounds of Claim 2.

Modification of the Restriction Requirement to the extent discussed above is believed to be in order. Such action is respectfully requested.

II. FORMAL OBJECTIONS

At the top of page 4 of the action, the Examiner has indicated that should Claim 1 be found allowable, Claim 15 will be objected to as being a substantial duplicate. A similar position has been taken with respect to Claim 16. In response, and without

conceding to the merit of these objections, Claims 15 and 16 have been canceled without prejudice.

Claims 1 and 3-20 have been objected to as allegedly drawn to an improper Markush group. This rejection is respectfully traversed.

As noted earlier, the compounds of Claims 1-20 share a common nucleus in that they all bear a C_{1-3} alkyl substituent in one or more of the 2-, 4-, 6-, and 8-positions of the bispidine ring. Moreover, the compounds of Claims 1-20 all bear a phenyl-terminated alkylene group on one *N*-atom and an alkoxy carbonyl (or thiolatocarbonyl) function on the other. These common features clearly define a "common nucleus," and thus do not constitute an improper Markush group. Reconsideration and withdrawal of this aspect of the formal rejection are accordingly respectfully requested.

III. THE 35 U.S.C. 112, SECOND PARAGRAPH, REJECTION

Claims 11, 13, 14 and 20 (in part) stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for the reasons discussed on page 5 of the action. That rejection is respectfully traversed.

Claim 20 has been objected to on the ground that the term "derivative" is allegedly indefinite. The Examiner states that it is "unclear as to the compounds being claimed." In response, it is noted that Claim 20 relates to a **proc ss** for preparing

compounds of formula I and does not claim any compounds whatsoever. Moreover, while the Examiner has not specified which part of Claim 20 the objection is raised against, it is assumed that part (u) (which mentions a "protected derivative" of a compound of formula I) is the section referred to by the Examiner. Clarification in this regard from the Examiner is respectfully requested.

If the Examiner's objection is directed to part (u) of Claim 20, it is noted that "protected derivative" is language which will be completely clear to one of ordinary skill in this art. A person of ordinary skill will appreciate that a protected derivative of a compound of Formula I will be a compound that can be converted, in a simple deprotection step, to a compound of formula I. Moreover, the person of ordinary skill would be well aware of a large number of protective groups which may be used to protect the functional groups present in compounds of formula I (such as protective groups disclosed in the books mentioned at page 37, lines 5-8 of the application as originally filed). Should the Applicants be forced to specify exact structures of the protected compounds used in step (u) of Claim 20, the claim would no longer provide the Applicants with the proper protection for their invention. That is, in hindsight of the disclosure of the invention, it would be a trivial matter for one of ordinary skill to use any given protective group in the process of part (u) of original Claim 20, thus making it easy for one of ordinary skill to avoid the claim if it is limited with respect to the structure of the protected derivative. Withdrawal of this aspect of the formal rejection is accordingly respectfully requested.

Claims 13 and 14 have been objected to in that they do not refer to an effective amount of the compound of formula I. In response, Claim 14 has been canceled without prejudice in that it is directed to a "use," and Claim 13 has been amended to include reference to "an effective amount." Withdrawal of this aspect of the formal rejection is respectfully requested.

Claim 1 lines 4-6 and occurrences in Claims 3-20 which are optionally substituted and/or terminated (as appropriate) by one or more substituents have been objected to as allegedly vague and indefinite. In response, the claims have been amended to amend this language to delete "and/or terminated (as appropriate)." Withdrawal of this aspect of the formal rejection is accordingly respectfully requested.

The Examiner has objected to the expression "(as appropriate)" as allegedly vague and ambiguous. It is not understood what is vague and ambiguous about this expression. One of ordinary skill would have no difficulty in understanding that expression in the context of the immediately preceding language in the claim. Reconsideration of this aspect of the formal rejection is therefore respectfully requested.

Claim 1, lines 22 and 23 and other occurrences throughout Claims 3-20 have been objected to in regard to the phrase "(which latter three groups ...)" is allegedly indefinite. It is not understood why this objection has been made. It is clear that, for example, the term "which latter three groups" refers to the last three groups that have

been previously mentioned. In the example cited by the Examiner, it is therefore clear from the wording of the application as filed that, for the group "A":

(i) the -$(CH_2)_m$-group of -$N(R^{25})(CH_2)_m$-, -$O(CH_2)_m$- or -$(CH_2)_mC(H)(OR^{25})(CH_2)_n$- is attached to the bispidine N-atom; and

(ii) each of C_{1-6} alkyl, -$N(R^{25})(CH_2)_m$-, -$O(CH_2)_m$- or -$(CH_2)_mC(H)(OR^{25})(CH_2)_n$- is optionally substituted by one or more OH groups.

The above facts are clearly expressed in Claim 1 as presently worded. It is not seen how this definitional language can be presented in a form which is clearer than this. Indeed, the alternative wording suggested by the Examiner appears to be considerably less clear. That is, it appears that the Examiner is suggesting recasting the definition of "A" such that it reads :

A is -$NR^{25})(CH_2)_m$-, -$O(CH_2)_m$- or -$(CH_2)_mC(H)(OR^{25})(CH_2)_n$-, or C_{1-6} alkyl, -$N(R^{25})(CH_2)_m$-, -$O(CH_2)_m$- and -$(CH_2)_mC(H)(OR^{25})(CH_2)_n$- which are optionally substituted with one or more OH groups, or -$N(R^{25})(CH_2)_m$-, -$O(CH_2)_m$- and -$(CH_2)_mC(H)(OR^{25})(CH_2)_n$- which are attached to the bispidine nitrogen...".

Apart from the fact that this definition is unnecessarily repetitious, it makes no sense (for example in the situation that "A" can represent more than one group) and, moreover, it does not appear to describe the same subject matter as described by the current definition of "A". In this respect, this is unacceptable to the applicants.

Claim 11 has been objected to in regard to the phrase "in which latter two cases p is 1, 2 or 3)" is allegedly indefinite. Again, it is not understood how the use of the word "latter" gives rise to any lack of clarity. The wording of Claim 11

is perfectly clear and precise in specifying that, when B represents $-(CH_2)_pO-$ or $-(CH_2)_pN(R^{26})-$, p is 1, 2 or 3. Moreover, should "in which latter two cases" be replaced by "wherein," there would be ambiguity as to whether the restricted definition of "p" applied to $-(CH_2)_pN(R^{26})-$ alone or to both $-(CH_2)_pO-$ and $-(CH_2)_pN(R^{26})-$. Claim 1 as presently worded is considerably clearer and less ambiguous than the alternative wording suggested by the Examiner.

Reconsideration of this aspect of the formal rejection is believed to be in order. Such action is respectfully requested.

Claim 19 has been objected to in regard to the phrase "to a person suffering from, or susceptible to, such a condition." In response, Claim 19 has been amended to replace the language objected to by the Examiner by "to a patient in need thereof." Withdrawal of this aspect of the formal rejection is now respectfully requested.

Claims 17 and 18 have been objected to in view of use of the term "use." In response, Claim 17 has been canceled without prejudice, and Claim 18 has been re-presented as a new method claim dependent on present Claim 19. Withdrawal of the 35 U.S.C. 112, second paragraph, rejection is respectfully requested.

IV. THE OBVIOUSNESS REJECTION

Claims 1 and 3-20 stand rejected under rejected under 35 U.S.C. 103(a) as allegedly unpatentable over reference EP 0308843 to Lubisch et al. That rejection is respectfully traversed.

Attention is directed to the proviso (a) and (b) at page 58, lines 19-21 of the application as filed. As a result of those provisos, all of the compounds of Claim 1 bear a C_{1-3} alkyl substituent in one or more of the 2-, 4-, 6-, and 8-positions of the bispidine ring. EP 308843 describes only compounds that are unsubstituted at those positions. Moreover, the compounds of Claim 1 are all carbamates or thiocarbamates (due to the presence of the $C(O)XR^1$ group). EP 308843 describes solely amide and urea compounds (see the definition of the group "Y," which represents C(O) or C(O)NH only).

In light of the above, it is clear that EP 308843 does not disclose or suggest the compounds as claimed in Claim 1. There would have been no motivation for one of ordinary skill to resort to that disclosure in the context of the presently claimed invention. Even if that did occur, it is clear that the presently claimed invention would not have resulted or have been rendered obvious thereby. Reconsideration and withdrawal of the outstanding obviousness rejection based on Lubisch et al are accordingly respectfully requested.

V. INFORMATION DISCLOSURE STATEMENT

Attached is a completed PTO-1449 listing U.S. Patent No. 6,291,475, together with a copy of that patent and the requisite IDS check ($180.00). The Examiner is requested to initial the attached PTO-1449 and to return a copy of the initialed document to the undersigned with the next paper to issue in this application.

It is noted with appreciation that the IDS submissions of February 20, 2001 and December 5, 2001. However, it is noted that the Examiner has not acknowledged the IDS dated August 30, 2001. The Examiner is requested to acknowledge receipt of that document and return a copy of the initial PTO-1449 to the undersigned with the next paper to issue in this application.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

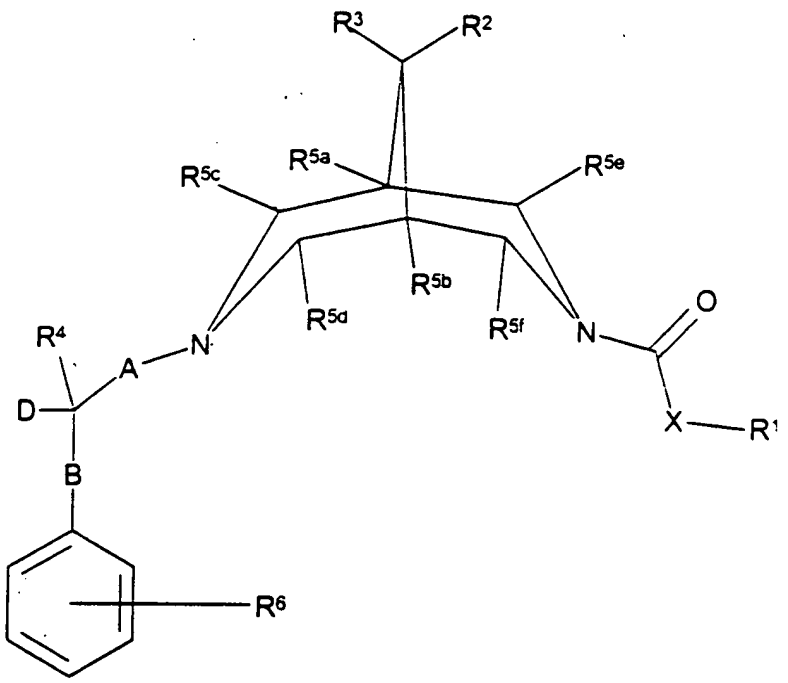
By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lks
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. (Amended) A compound of formula I



I

wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$-aryl, or $-(CH_2)_a$-Het^1 (all of which are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from the group consisting of -OH, halo, cyano, nitro, C_{1-4} alkyl [and/or] and C_{1-4} alkoxy);

a represents 0, 1, 2, 3, or 4;

Het^1 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen [and/or] and sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e} and R^{5f} independently represent H or C_{1-3} alkyl;

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted [and/or terminated] with one or more nitro or cyano groups), OR^7, $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$

R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$-aryl (which latter two groups are optionally substituted [and/or terminated] by one or more substituents selected from the group consisting of -OH, halo, cyano, nitro, C_{1-4} alkyl [and/or] and C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;

b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, C_{1-4} alkyl, $-OR^9$, or $-(CH_2)_cN(R^{10})(R^{11})$;

R^9 represents H, C_{1-6} alkyl, $-C(O)R^{12}$, $-(CH_2)_d$-aryl or $-(CH_2)_d$-Het^2 (which latter three groups are optionally substituted by one or more substituents selected from the group consisting of -OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)R^{13}$, $C(O)OR^{14}$ [and/or] and $-N(H)S(O)_eR^{15}$);

R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_f$aryl, $-C(NH)NH_2$, $-S(O)_2R^{15a}$, $-[C(O)]_gN(R^{16})(R^{17})$, $C(O)R^{18}$ or $-C(O)OR^{19}$;

e represents 0, 1 or 2;

g [represent] represents 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{20}$ or $-(CH_2)_h$-aryl (which latter group is optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from the group consisting of -OH, cyano, halo, amino, nitro, $C_{,6}$ alkyl [and/or] and $C_{,6}$ alkoxy);

R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} independently represent H, C_{1-6} alkyl, Het^3 or -$(CH_2)_j$-aryl (which latter three groups are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from the group consisting of -OH, cyano, halo, amino, nitro, C_{1-6} alkyl [and/or] and C_{1-6} alkoxy);

R^{15} and R^{15a} independently represent C_{1-6} alkyl, aryl or -$(CH_2)_k$-aryl (all of which are all optionally substituted [and/or terminated (as appropriate)] by one or more substituents [chosen] selected from the group consisting of halo, nitro, C_{1-6} alkyl [and/or] and C_{1-6} alkoxy);

c, d, f, h, j and k independently represent 0, 1, 2, 3 or 4;

Het^2 and Het^3 independently represent five to ten-membered heterocyclic rings containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen [and/or] and sulfur, and which also optionally includes one or more =O substituents;

R^6 represents one or more optional substituents selected from the group consisting of -OH, cyano, halo, amino, nitro, C_{1-6} alkyl (optionally terminated by $N(H)C(O)OR^{20a}$), C_{1-6} alkoxy, $-C(O)N(H)R^{21}$, $-NHC(O)N(H)R^{22}$, $-N(H)S(O)_2R^{23}$ [and/or] and $-OS(O)_2R^{24}$;

R^{21} and R^{22} independently represent H or C_{1-6} alkyl;

R^{20a}, R^{23} and R^{24} independently represent C_{1-6} alkyl;

A represents a single bond, C_{1-6} alkylene, $N(R^{25})(CH_2)_m$, $O(CH_2)_m$ or $(CH_2)_mC(H)(OR^{25})(CH_2)_n$- (in which latter three groups, the -$(CH_2)_m$- group is attached to the bispidine nitrogen atom and which latter four groups are optionally substituted by one or more -OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_pN(R^{26})-$, $-(CH_2)_pS(O)_q-$, $-(CH_2)_pO-$ (in which three latter groups, the $-(CH_2)_p-$ group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{26})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R^4),

$-N(R^{26})C(O)O(CH_2)_p-$ or $-N(R^{26})(CH_2)_p-$ (in which latter two groups, the $N(R^{26})$ group is attached to the carbon atom bearing D and R^4); m, n and p independently represent 0, 1, 2, 3 or 4;

q represents 0, 1 or 2;

R^{25} represents H, C_{1-6} alkyl or $C(O)R^{27}$;

represents H or C_{1-6} alkyl;

R^{26} represents H or C_{1-6} alkyl;

R^{27} represents H, C_{1-6} alkyl, Het^4 or $-(CH_2)_r$-aryl (which latter two groups are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from the group consisting of -OH, cyano, halo, amino, nitro, C_{1-6} alkyl [and/or] and C_{1-6} alkoxy);

Het^4 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen [and/or] and sulfur, and which also optionally includes one or more =O substituents;

r represents 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative thereof;

provided that:

(a) R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e} and R^{5f} do not all simultaneously represent H;

(b) R^{5a} and R^{5b} do not represent C_{1-3} alkyl when R^{5c}, R^{5d}, R^{5} , and R^{5f}, all represent H; and

(c) when D represents -OH or —$(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then: -

(i) A does not represent $N(R^{25})(CH_2)_m$, $O(CH_2)_m$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ (in which n is 0); and/or

(ii) p does not represent 0 when B represents —$(CH_2)_pN(R^{26})-$, $-(CH_2)_pS(O)_q$ or —$(CH_2)_pO-$.

13. (Twice Amended) A pharmaceutical formulation including an effective amount of a compound as defined in Claim 1 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

19. (Twice Amended) A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in Claim 1 to a [person suffering from, or susceptible to, such a condition] to a patient in need thereof.